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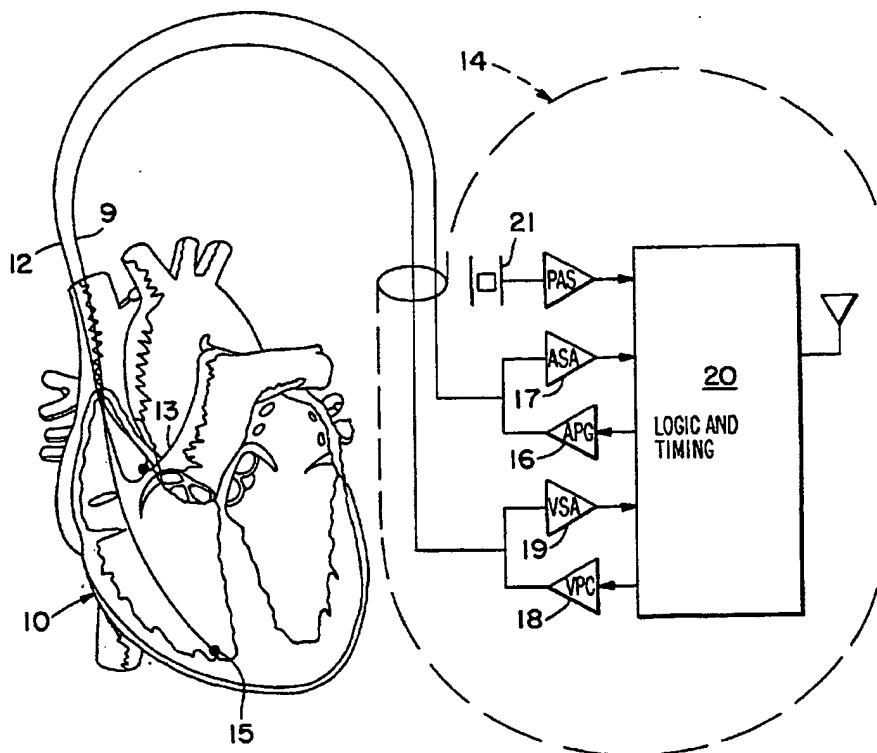
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(54) Title: SINUS PREFERENCE METHOD AND APPARATUS FOR CARDIAC PACEMAKERS

(57) Abstract

A dual chamber, rate-responsive pacemaker for pacing a patient's heart novelly allows tracking of the patient's sinus rate when the sinus rate is slightly less than the sensor rate; i.e., within a predetermined "Sinus Preference Window Maximum Rate Drop". Pacing at the sensor rate occurs when the sensor rate exceeds the sinus rate by more than the Sinus Preference Window Maximum Rate Drop. In the preferred embodiment a Sinus Preference Window, which occurs at the end of the ventricle-to-atrium interval, is decremented with successive heart beats by a programmable Δ to increase the pacing rate until the Sinus Preference Window reaches zero, in which case the pacemaker paces at the sensor rate. The Sinus Preference

Window is reset to its maximum value upon either the detection of an atrial sensed event, or upon the expiration of a programmable Sinus Check Interval. The pacemaker paces at the sinus rate or the maximum rate drop rate, whichever is faster, for a number of recovery beats, and then increments the pacing rate up to the sensor rate.



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SINUS PREFERENCE METHOD AND APPARATUS FOR CARDIAC PACEMAKERS

Background of the Invention

5 1. Field of the Invention

The present invention relates to dual chamber, rate-responsive pacemakers.

2. Description of the Prior Art

10 Dual chamber pacing modes have been widely adopted for pacing therapy. Among the dual chamber operating modes is the "DDD" mode, which can pace an atrium and a ventricle, senses both the atrium and the ventricle, and can either inhibit or trigger pacing stimuli for both chambers. This mode has a sensor augmented variant mode called "DDDR",
15 where the "R" stands for rate-adaptive or rate modulation.

A DDD pacemaker includes an atrial sense amplifier to detect atrial depolarizations of the heart, and a ventricular sense amplifier to detect ventricular depolarizations of the heart. If the atrium of the heart
20 fails to beat within a predefined time interval (atrial escape interval), the pacemaker supplies an atrial stimulus to the atrium through an appropriate lead system. Following an atrial event (either sensed or paced) and an atrioventricular (AV) interval, the pacemaker supplies a
25 ventricular pacing stimulus to the ventricle through an appropriate lead system, if the ventricle fails to depolarize on its own. Pacemakers which perform this function have the capability of tracking the patient's natural sinus rhythm and preserving the hemodynamic
30 contribution of the atrial contraction over a wide range of heart rates.

Many patients have an intact sinoatrial (SA) node, but inadequate AV conduction. For these patients, the DDD mode, which attempts to pace the ventricles in synchrony
35 with the atria, is generally adequate for their needs. Patients with Sick Sinus Syndrome (SSS) have an atrial rate which can either be sometimes appropriate, sometimes too fast, and sometimes too slow. For SSS patients, the DDDR mode provides some relief by pacing the atria and

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ventricles at a sensor rate determined by a sensor which senses a physiological indicator of the patients' metabolic needs. However, sensor rates are sometimes too high and sometimes too low for a variety of reasons, including, errors related to the input of programmable parameters, limitations of the sensor's ability to accurately sense the physical quantity being sensed, and limitations or problems with the algorithm used to determine the sensor rate.

In addition to the above problems, pacemakers operating in prior art sensor driven pacing modes pace at the sensor rate (and overdrive the atrium) whenever the sensor rate exceeds the sinus rate, even when the sinus rate is actually appropriate, and even when the difference between the two rates is too small to provide any discernible benefit in pacing at the higher sensor rate. Inappropriate sensor rate pacing can lead to unnecessary overdrive of the atrium, and unwarranted expenditure of battery energy.

Summary of the Invention

In view of the above, it is an object of the present invention to provide a novel dual chamber pacemaker with rate modulation capabilities, which does not overdrive the atrium with a higher sensor rate, when the sinus rate is appropriate for the current physiologic demand on the patient's heart.

There is provided in accordance with the present invention, a rate-responsive pacemaker for pacing a patient's heart at a pacing rate, at least including:

atrial pace stimulator means for generating an atrial pacing stimulus when needed;

atrial sensing means for generating an atrial sensed event signal in response to a depolarization of atrial tissue;

ventricular pace stimulator means coupled to the atrial pace stimulator means and the atrial sensing means for generating a ventricular pacing stimulus following an atrioventricular interval; and

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sensor rate means coupled to the atrial pace
stimulator means for deriving a sensor rate related to
physiologic demand on the heart;

wherein the pacing rate tracks the patient's sinus
rate unless the sensor rate exceeds the sinus rate by a
predetermined margin, in which case the pacing rate is
changed to the sensor rate.

There is also provided in accordance with the present
invention, a pacing method for pacing a patient's heart
with a rate-responsive pacemaker at a pacing rate, at least
including the steps of:

generating an atrial pacing stimulus when needed;

generating an atrial sensed event signal in response
to a depolarization of atrial tissue;

generating a ventricular pacing stimulus following an
atrioventricular interval; and

deriving a sensor rate related to physiologic demand
on the heart;

wherein the pacing rate tracks the patient's sinus
rate unless the sensor rate exceeds the sinus rate by a
predetermined margin, in which case the pacing rate is
changed to the sensor rate.

The details of the present invention will be revealed
in the following description, with reference to the
attached drawing.

Brief Description of the Drawing

In the various figures of the drawing, like reference
numerals indicate identical structures throughout the
several views, and the elements are numbered such that the
leftmost digit corresponds to the drawing figure in which
an element first appears.

Figure 1 is block level diagram of a DDDR pacemaker
capable of implementing the Sinus Preference Algorithm of
the present invention.

Figure 2 is a timing diagram depicting Sinus
Preference Windows of the present invention in response to
atrial paced and sensed events;

Figure 3 is a continuation of the timing diagram in
Figure 2.

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Figure 4 is a graph of heart rate versus time using the Sinus Preference Algorithm of the present invention.

Figure 5 is a resulting electrocardiogram in response to changing Sinus Preference Windows and the occurrence of atrial sensed events.

Figure 6 is a graph of ventricular rate versus time, illustrating several recovery beats after the maximum rate drop has been reached.

Detailed Description of the Preferred Embodiment

The present invention may be incorporated into such prior art pacemakers as, for example, DDD pacemaker taught by U.S. Patent 4,312,355 to Funke, hereby incorporated by reference. Another rate-responsive pacemaker suitable for use with the invention is taught in U.S. Patent 4,951,667 to Markowitz et.al., hereby incorporated by reference, which teaches a dual chamber, activity-based, rate-responsive pacemaker of the DDDR type. This pacemaker utilizes sensed patient activity to set the pacemaker's "sensor" rate.

Figure 1 is block level diagram which sets forth the structures required to incorporate the invention into a DDD/DDDR pacemaker. In the drawing, the patient's heart has an atrial pacing lead 12 passed into the right atrium and a ventricular lead 9 passed into the right ventricle. The atrial lead 12 has an atrial electrode array 13 which couples the pacemaker 14 to the atrium. The ventricular lead 9 has a ventricular electrode array 15 for coupling the pacemaker 14 to the ventricular tissue of a patient's heart 10.

The atrial electrode array 13 is coupled to both an atrial pace stimulus generator 16 (APG), and an atrial sense amplifier 17 (ASA). In a similar fashion, the ventricular electrode array 15 is coupled to a ventricular pace stimulus generator 18 (VPG) and a ventricular sense amplifier 19 (VSA). Although the arrangement in Figure 1 uses a bipolar configuration, it can be easily modified to use a bipolar configuration, as well.

Figure 1 shows a preferred patient activity sensor (PAS) 21 and appropriate signal conditioning circuitry,

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which can be provided to alter the pacemaker operation in response to the sensed motion of the patient. An appropriate activity-based, rate-responsive system is taught by U.S. Patent 4,428,378 to Anderson et al., which is incorporated by reference herein. It should be appreciated that alternate sensors can be provided to achieve rate and postventricular atrial refractory period (PVARP) variation based upon other sensed physical parameters.

In general, the atrial sense amplifier ASA 17 detects depolarizations of atrial tissue and generates an atrial sensed event (ASE) to indicate the detection of an atrial beat of the patient's heart. Similarly, the ventricular sense amplifier VSA 19 responds to a ventricular beat of the patient's heart and generates a corresponding ventricular sensed event (VSE).

The pacemaker logic 20, which is coupled to the sense amplifiers, generates various time intervals in response to detected atrial and ventricular sensed events, and generates both atrial paced event and ventricular paced event signals in response to timer logic and the sense amplifier signals. The principal timing functions are set forth in Table 1, below.

Timer	Starting Events(s)	Ending Event(s)
PPVARP	VPE or VSE	Timeout
V-A (DDDR) or V-A (DDD)	VSE or VPE	APE
URL	VSE or VPE	Timeout
AVD	APE or ASE	VPE or VSE
RLI	VSE or VPE	Timeout
Disable Interval (T)	VPE	Timeout

TABLE 1
Timing Functions

For example, timer logic 20 is provided with means to time out a programmed AV delay period (AVD). The AV delay period is initiated by the occurrence of either an atrial

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sensed or atrial paced event. The AV delay period may end with the generation of a ventricular paced event (VPE).

Logic 20 also provides for a programmed post ventricular atrial refractory period (PPVARP). The PPVARP period begins with either a ventricular paced event (VPE) or a ventricular sensed event (VSE), and expires at the conclusion of a physician-set time interval.

The logic also times out a refractory limit interval (RLI) which begins with the occurrence of a ventricular sensed or paced event. Pacemaker logic 20 also times out a disable interval period of a fixed but physician-selected duration. This disable interval time period begins upon the occurrence of a ventricular paced event (VPE) in a pacemaker cycle where the next post ventricular atrial refractory period is extended. Pacemaker logic 20 times out an upper rate limit interval (URL). This timer is initiated by the occurrence of a ventricular paced event (VPE) or ventricular sensed event (VSE), and limits the upper rate at which ventricular stimuli are delivered to the heart. Preferably two separate lower rate interval timer functions are provided. The first is set by the physician when the base pacing rate is selected. This DDD V-A time interval starts from the occurrence of a ventricular sensed event (VSE) or ventricular paced event (VPE), and provided neither an ASE nor a VSE occurs during the V-A time interval, an atrial paced event (APE) is generated after the expiration of the V-A time interval. The duration of the second lower rate time interval is a function of the measured patient activity acquired by the activity sensor 21. Typically, this DDDR V-A time interval begins with a sensed or paced ventricular event (VSE or VPE, respectively) and has a time duration reflecting patient activity. In this art, such structures are well known, and a variety of techniques can be used to implement the required timer functions.

The pacemaker logic 20 is also coupled to paced event pulse generators. For example, atrial paced event signals are coupled to the atrial pace stimulus generator 16 to produce an atrial pacing stimulus while the ventricular

paced event signal generates a ventricular pacing stimulus through the ventricular pace stimulus pulse generator 18.

Summary of the Sinus Preference Algorithm Operation

5 As with prior art pacemakers, a pacemaker employing the Sinus Preference Algorithm of the present invention, a unique variant of the DDDR mode, tracks the sinus rate when the sinus rate exceeds the sensor rate. Unlike prior art
10 pacing algorithms, the Sinus Preference Algorithm does not always cause the pacemaker to pace whenever the sensor rate exceeds the sinus rate. The pacemaker 14 paces at the sensor rate, or a variation thereof, whenever the sensor rate exceeds the sinus rate by more than a programmable maximum rate drop. Otherwise, the pacemaker 14 tracks the sinus rate. The Sinus Preference Algorithm will be
15 explained in greater detail *infra.*, with reference to Figures 2-6.

Details of the Sinus Preference Algorithm Operation

20 Figures 2 and 3 together, represent a timing diagram of an example of successive heart cycles which illustrate the operation of the present invention. At the beginning of the timing diagram, a ventricular paced event (VPE) occurs after an atrial paced event (APE) and a paced atrioventricular (PAV) interval. At this point in time, the pacemaker 14 paces at the sensor rate. After a sensor-
25 derived ventricle-to-atrium (V-A) interval (also the atrial escape interval at this time), the pacemaker 14 again delivers a pacing stimulus to the atrium. Following a PAV, the pacemaker 14 delivers a pacing stimulus signal to the ventricle.

30 In the example, an atrial sensed event (ASE) occurs after a measured V-A interval (less than the sensor-derived V-A interval in this instance), followed by a sensed atrioventricular (SAV) interval and a VPE. The occurrence of the first ASE causes the algorithm to redefine the next
35 atrial escape interval. First, the previous measured V-A interval is compared to the sensor-derived V-A interval. If the sensor-derived V-A interval is the lesser of the two, the new atrial escape interval is set equal to the sensor-derived V-A interval plus the current SPW (in this

instance, MaxSPW). If the previous measured V-A interval is the lesser of the two, the algorithm then compares the sum of the previous measured V-A interval plus the previous SPW with the sensor-derived V-A interval. The greater of
5 the two is chosen as the new atrial escape interval. The first Sinus Preference Window SPW_1 is set to correspond to the programmed maximum rate drop (MaxSPW) from the sensor rate allowable.

The Sinus Preference Algorithm endeavors to first pace
10 at the sensor rate minus the maximum rate drop, to look for possible ASEs, thus searching for sinus node beats occurring within acceptable proximity to the sensor rate. If found, the pacemaker 14 then endeavors to track the sinus rate. Absent the above, the pacing rate remains at
15 the maximum rate drop level for several recovery beats, as shown in Figure 6. At each succeeding heart cycle, the pacing rate is increased by a programmable "SPW Rate Change". From the SPW Rate Change, a corresponding δ is derived, where δ equals the inverse of SPW Rate
20 Change, or the change in interval needed to accomplish the desired rate change. The δ is subtracted from each succeeding SPW.

The pacing rate is incremented each heart cycle by the SPW Rate Change until the sensor rate is reached, where the
25 pacemaker 14 continues to pace until either an ASE occurs, or a programmable Sinus Check Interval (SCI) spanning several heart cycles expires.

Returning to the timing diagram in Figure 2, a second ASE occurs prior to the expiration of the new atrial escape
30 interval; thus, the next Sinus Preference Window SPW_2 remains at MaxSPW, and the new atrial escape interval is chosen as described *supra*. Since no ASE occurs during the atrial escape interval, an APE occurs at its expiration followed in time by a VPE (see Figure 3).

35 The algorithm paces at the level resulting from the maximum rate drop for several recovery beats (not shown in Figure 3). Then, the pacing rate begins to increment by the SPW Rate Change, so that the SPW is decremented by δ . Thus, SPW_3 equals SPW_2 minus δ , and SPW_4 equals

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SPW₃ minus delta. However, prior to the expiration of the atrial escape interval that includes SPW₄, an ASE occurs, which resets SPW₅ to MaxSPW.

5 The effect of the Sinus Preference Algorithm is illustrated by the example in Figure 4, which shows graphs of heart rate versus time for p-wave or sinus rate (dotted curve), sensor rate (dashed curve), and A-V pacing rate (solid curve). In the range of heart rates where sinus tracking is appropriate ("Sinus Appropriate"), the sensor rate does not exceed the sinus rate by more than the SPW
10 Maximum Rate Drop. In the range of heart rates where sensor tracking is appropriate ("Sinus Not Appropriate"), the sensor rate exceeds the sinus rate by more than the SPW Maximum Rate Drop.

15 Once the SPW Maximum Rate Drop is exceeded (i.e., the pacemaker 14 reaches the end of the atrial escape interval without the occurrence of an ASE), and after the recovery beats, the pacemaker 14 begins incrementing the pacing rate until it reaches the sensor rate, where it remains until
20 either the expiration of the SCI or the occurrence of an ASE. The SCI is reset to zero, and begins counting each time the SPW is reset to MaxSPW. The SCI expires when its programmed maximum count is reached. The occurrence of an ASE might be interpreted as the return of the sinus rate to
25 an appropriate one for the current physiologic demand on the heart, to which the pacemaker 14 can then begin tracking again.

To further illustrate the operation of the Sinus Preference Algorithm, Figure 5 shows an example of an
30 electrocardiogram (ECG) and corresponding SPWs resulting from the occurrence of two ASEs.

Variations and modifications to the present invention may be possible given the above disclosure. However, all
35 such variations and modifications are intended to be within the scope of the invention claimed by this letters patent. For example, the present invention is not limited to any particular pacing mode, and can function with prior art modes such as DDDR, AAIR, VVIR and DDIR.

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We claim:

1. A pacemaker for pacing a patient's heart comprising:

5 pulse generator means for generating pacing pulses and applying said pulses to a chamber of a patient's heart;

sensing means for sensing depolarizations of said chamber of said patient's heart;

means for defining first escape intervals;

10 means responsive to sensing of a depolarization of said chamber of said patient's heart, for adding incremental intervals to said first escape intervals to define effective escape intervals;

means for triggering generation of a pacing pulse on expirations of said effective escape intervals;

15 means responsive to failures to sense depolarizations of said chamber of said patient's heart within said effective escape intervals, for gradually decrementing duration of said incremental intervals, over a series of said effective escape intervals.

20 2. A pacemaker according to claim 1, wherein said means for defining said first escape intervals comprises means for determining physiologic demand on said patient's heart and means for defining first said first escape intervals as a function of physiologic demand on said patient's heart.

25 3. A pacemaker according to claim 2, wherein said means for determining physiologic demand comprises means for sensing a physiologic parameter indicative of physiologic demand.

30 4. A pacemaker according to claim 3 wherein said means for defining said first escape intervals comprises means for determining the sinus rate of said patient's heart.

35 5. A pacemaker according to claim 4, wherein said means for defining said first escape intervals comprises means for deriving sensor based escape intervals as a function of said physiologic parameter and means for deriving sinus rate based escape intervals, and means for selecting said sensor based escape intervals or said sinus

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rate based escape intervals to be said first escape intervals, as a function of the relative durations of said sensor based and atrial rate based escape intervals.

5 6. A pacemaker according to claim 5 wherein said means for selecting comprises means for selecting said sensor based escape intervals as said first escape intervals if said sensor based escape intervals exceed said sinus rate based escape intervals.

10 7. A pacemaker according to claim 5 or claim 6, wherein said means for selecting comprises means for selecting said sinus rate based escape intervals as said first escape intervals, if said sensor based escape intervals exceed said sinus rate based escape intervals by less than a predetermined amount.

15 8. A pacemaker according to claim 5 or claim 6 or claim 7, further comprising means for setting said effective escape intervals equal to said sensor based escape intervals if said sensor based escape intervals exceed said sinus rate based escape intervals by more than said predetermined amount.

20 9. A pacemaker according to any of claim 1 - 8 above, wherein said sensing means comprises means for sensing atrial depolarizations and wherein said pulse generator means comprises means for applying pacing pulses to an atrium of said patient's heart.

25 10. A pacemaker according to any of claims 1 - 9, above, wherein said responsive means comprises means for gradually decrementing duration of said incremental intervals, over a series of said effective escape intervals, until said incremental intervals equal zero and said effective escape intervals equal said first escape intervals.

30 11. A pacemaker for pacing a patient's heart comprising:

35 pulse generator means for generating pacing pulses and applying said pulses to a chamber of a patient's heart;

sensing means for sensing depolarizations of said chamber of said patient's heart;

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means for sensing a physiologic parameter indicative of physiologic demand on said patient's heart and for deriving sensor based escape intervals based on said physiologic parameter;

5 means for determining the sinus rate of said patient's heart and for defining sinus rate based escape intervals;

means for defining effective escape intervals as a function of said sinus rate based escape intervals if said sinus rate based escape intervals are less than said sensor based escape intervals by no more than a predetermined duration, and for defining said effective escape intervals as a function of said sensor based escape intervals if said sensor based escape intervals exceed said sinus rate based intervals by more than said predetermined duration; and

15 means for triggering generation of a pacing pulse on expirations of said effective escape intervals.

12. A pacemaker according to claim 11, wherein said means for defining said effective escape intervals comprises means for defining effective escape intervals equal to said sinus rate based escape intervals plus incremental intervals, if said sinus rate based escape intervals are less than said sensor based escape intervals by no more than a predetermined duration, and for defining said effective escape intervals equal to said sensor based escape intervals plus incremental intervals if said sensor based escape intervals exceed said sinus rate based intervals by more than said predetermined duration.

25 13. A pacemaker according to claim 11 or claim 12 wherein said means for defining effective escape intervals comprises means for defining said effective escape intervals as a function of said sensor based escape intervals if said sensor based escape intervals are less than said sinus rate based intervals.

30 14. A pacemaker according to claim 13 wherein said means for defining effective escape intervals comprises means for defining said effective escape intervals equal to said sensor based escape intervals if said sensor based escape intervals are less than said sinus rate based intervals.

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15. A pacemaker according to claim 12, further comprising

5 means responsive to failures to sense depolarizations of said chamber of said patient's heart within said effective escape intervals, for gradually decrementing duration of said incremental intervals, over a series of said effective escape intervals.

10 16. A pacemaker according to claim 15 wherein said responsive means comprises means for gradually decrementing duration of said incremental intervals, over a series of said effective escape intervals, until said incremental intervals equal zero.

15 17. A pacemaker according to any of claims 11 - 16 above, wherein said sensing means comprises means for sensing atrial depolarizations and wherein said pulse generator means comprises means for applying pacing pulses to an atrium of said patient's heart.

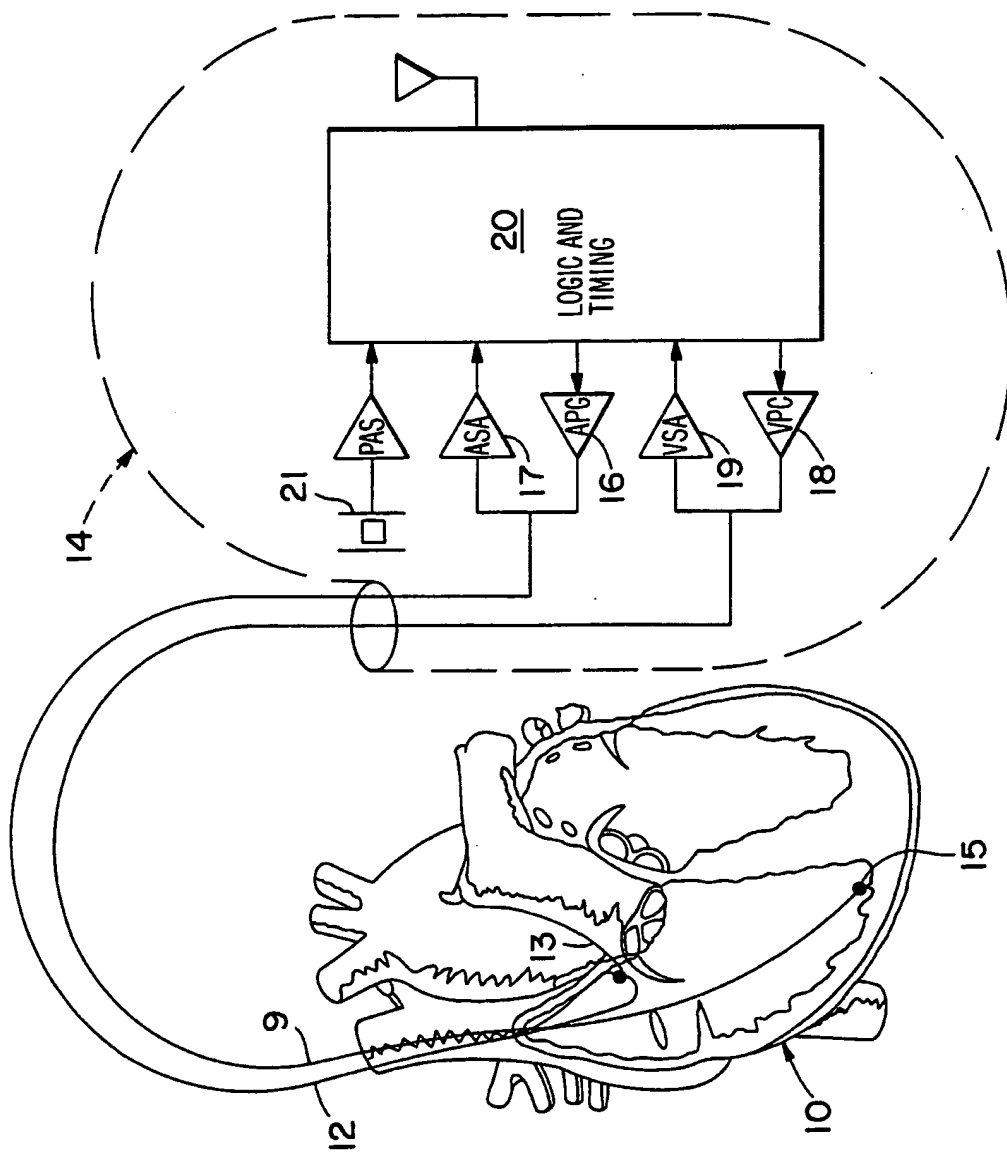


FIG. 1

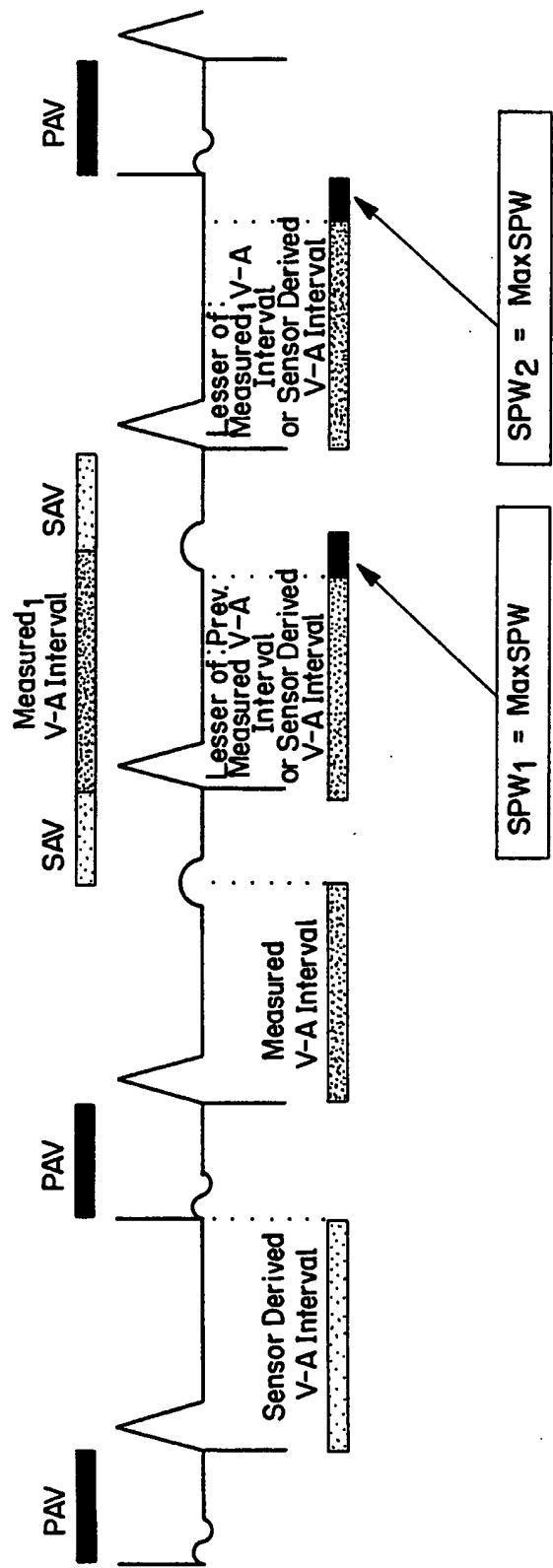


FIG. 2

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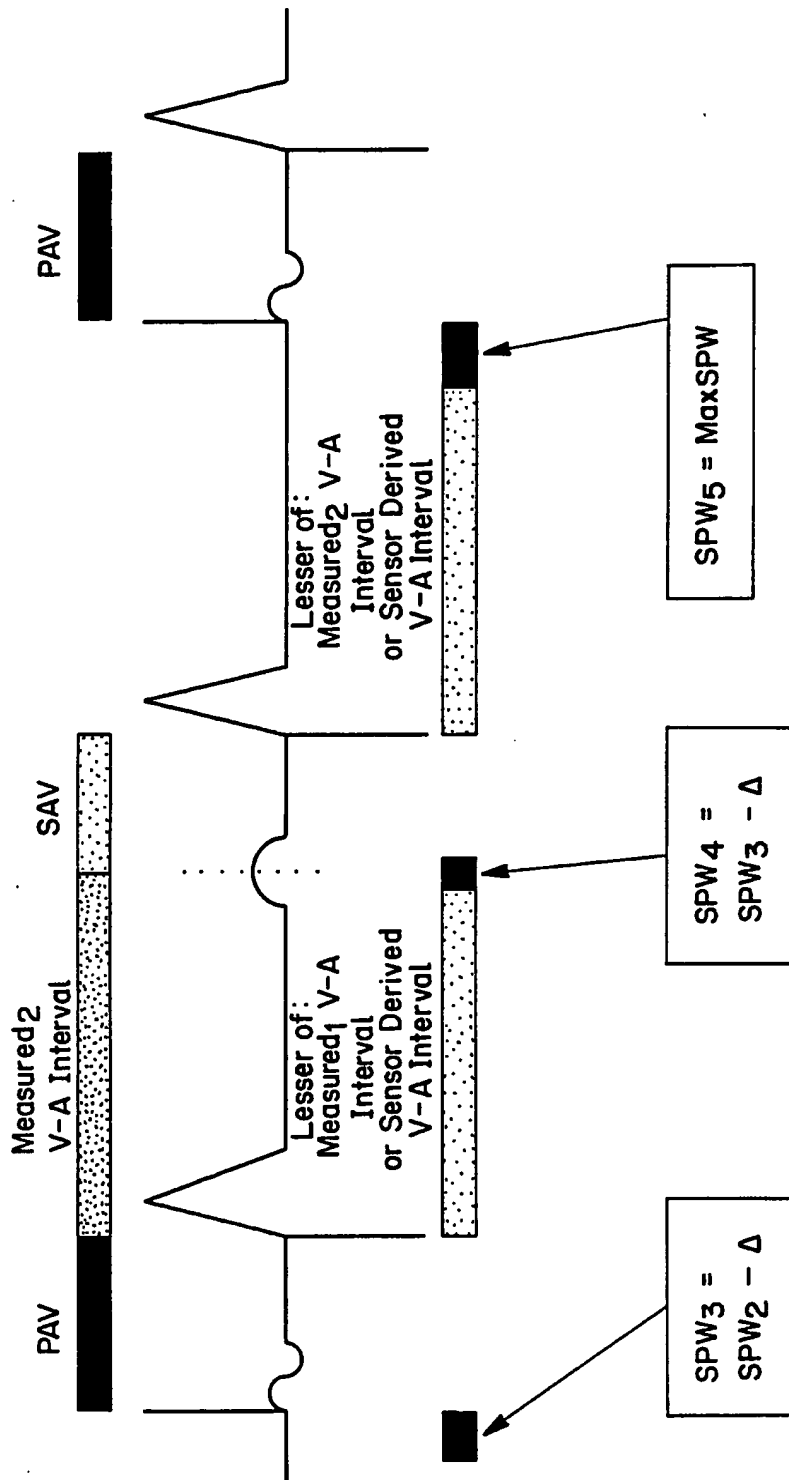


FIG. 3

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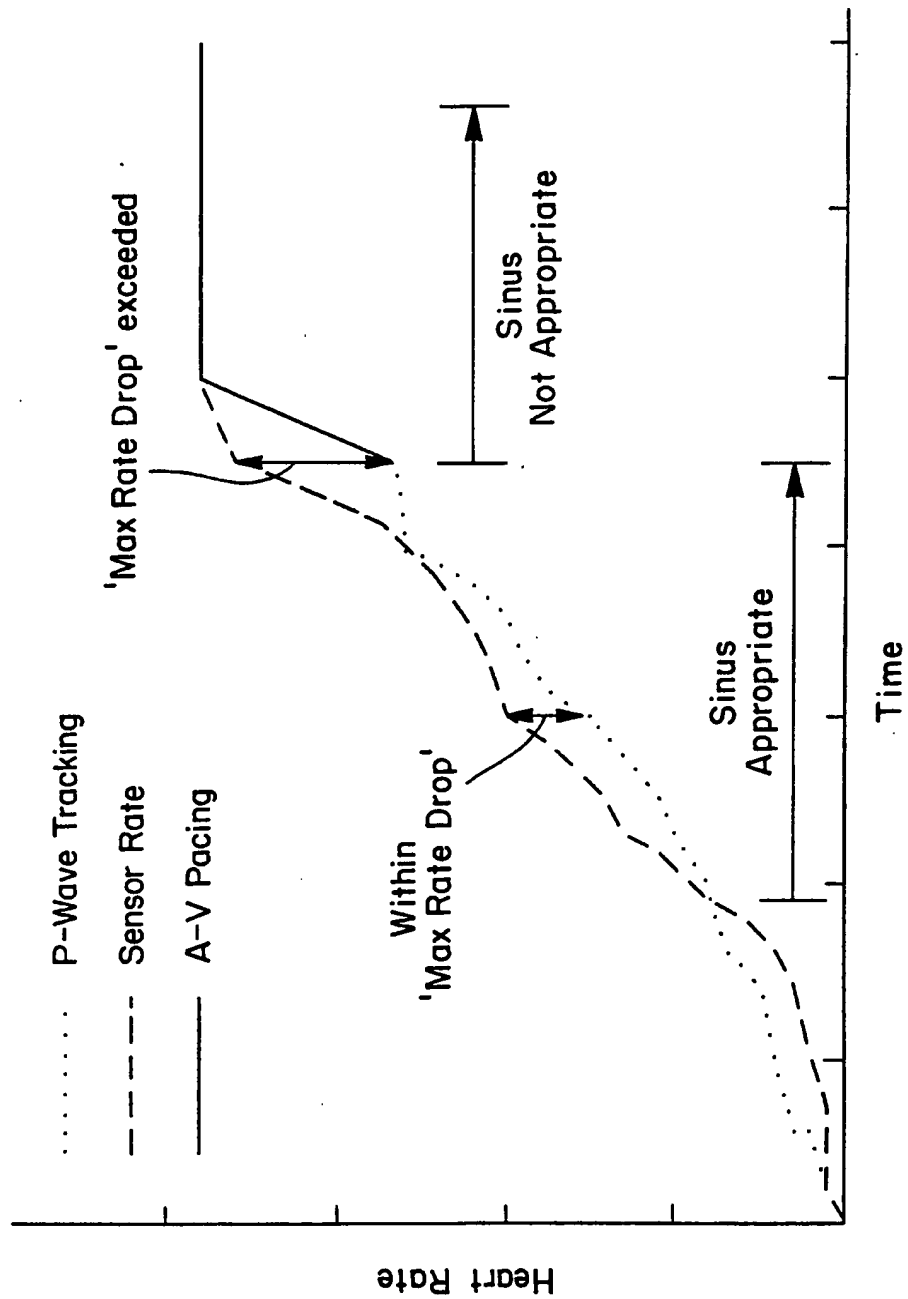


FIG. 4

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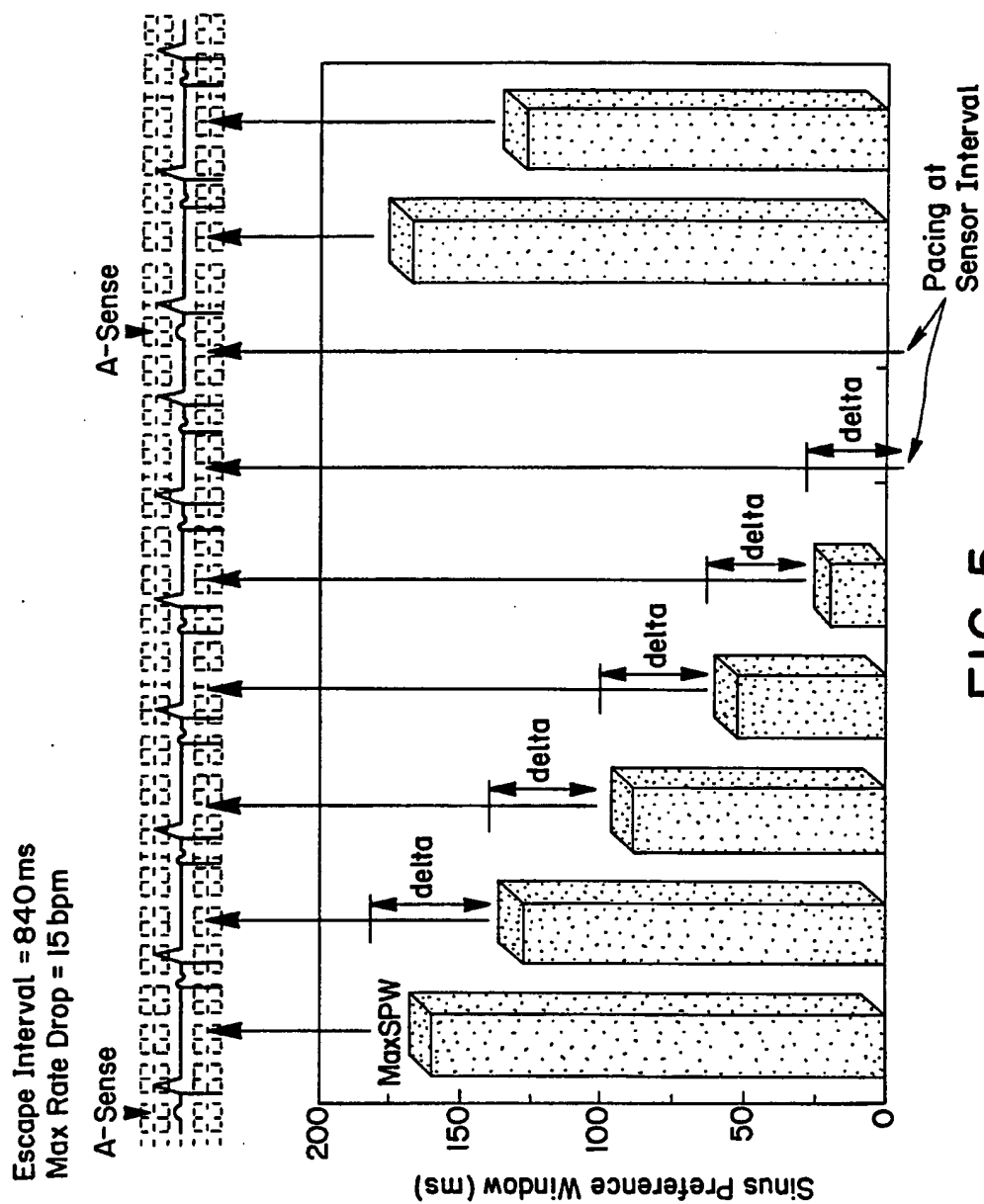


FIG. 5

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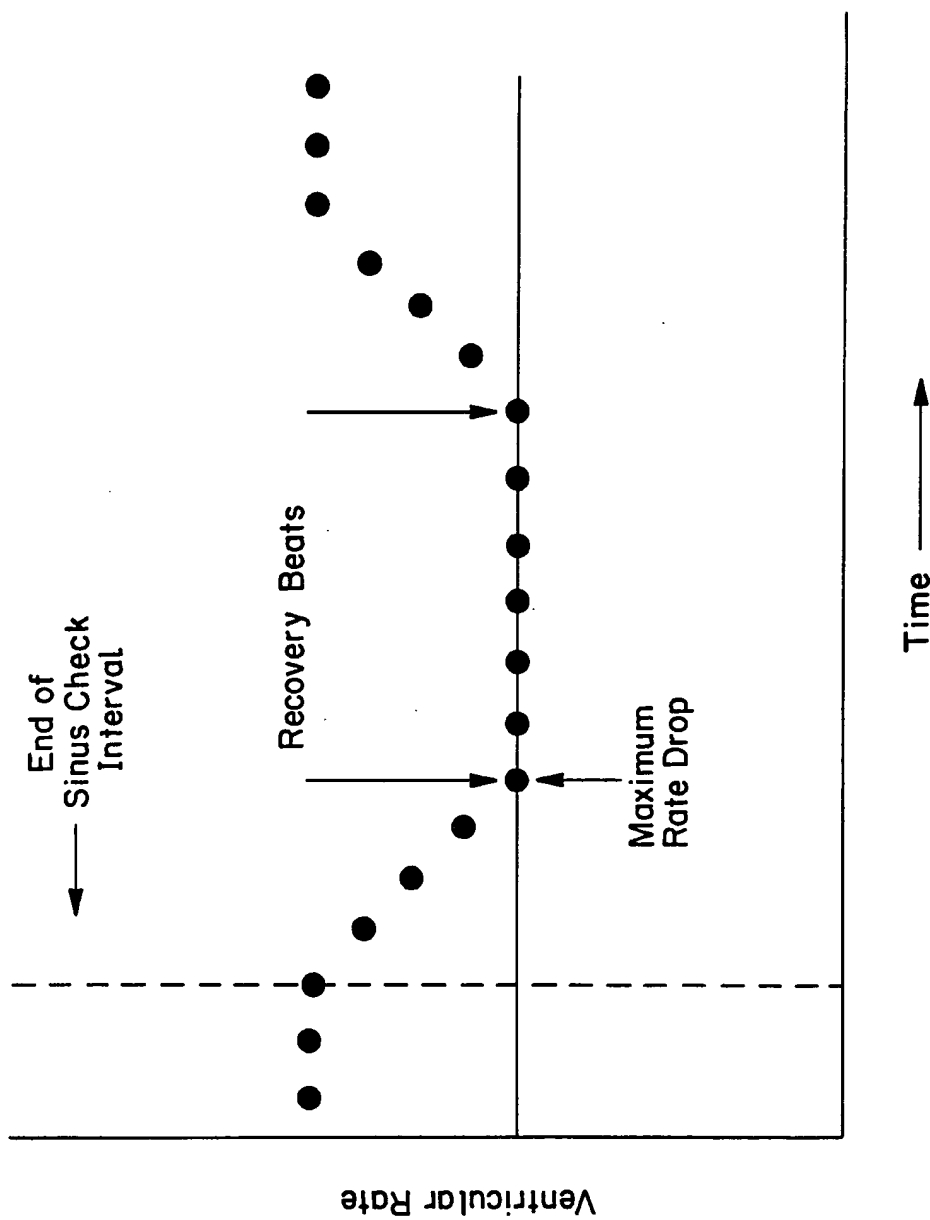


FIG. 6

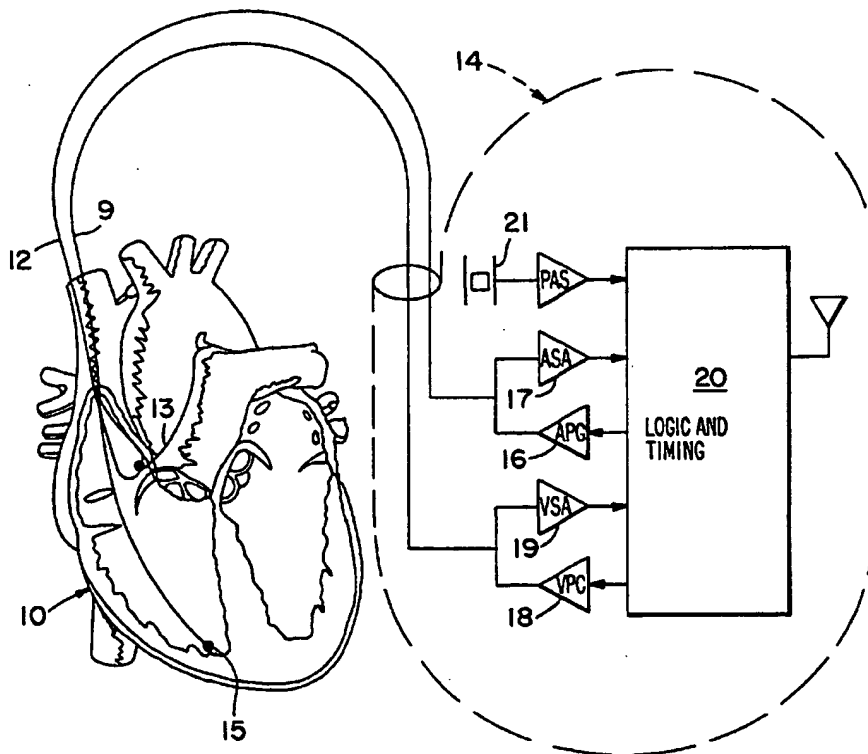
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(54) Title: SINUS PREFERENCE METHOD AND APPARATUS FOR CARDIAC PACEMAKERS

(57) Abstract

A dual chamber, rate-responsive pacemaker for pacing a patient's heart novelly allows tracking of the patient's sinus rate when the sinus rate is slightly less than the sensor rate; i.e., within a predetermined "Sinus Preference Window Maximum Rate Drop". Pacing at the sensor rate occurs when the sensor rate exceeds the sinus rate by more than the Sinus Preference Window Maximum Rate Drop. In the preferred embodiment a Sinus Preference Window, which occurs at the end of the ventricle-to-atrium interval, is decremented with successive heart beats by a programmable *delta* to increase the pacing rate until the Sinus Preference Window reaches zero, in which case the pacemaker paces at the sensor rate. The Sinus Preference



Window is reset to its maximum value upon either the detection of an atrial sensed event, or upon the expiration of a programmable Sinus Check Interval. The pacemaker paces at the sinus rate or the maximum rate drop rate, whichever is faster, for a number of recovery beats, and then increments the pacing rate up to the sensor rate.

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5085215 (TIBOR A. NAPPHOLZ ET AL), 4 February 1992 (04.02.92), column 4, line 62 - column 5, line 12, abstract --	1-17
A	US, A, 5144949 (WALTER H. OLSON), 8 Sept 1992 (08.09.92), figure 2, claim 1 --	1-17
A	US, A, 5342405 (JAMES L. DUNCAN), 30 August 1994 (30.08.94), column 6, line 6 - line 46 --	1-17

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

13 March 1995

Date of mailing of the international search report

12. 04. 95

Name and mailing address of the International Searching Authority



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/10158

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5350409 (GUSTAAF A. STOOP ET AL), 27 Sept 1994 (27.09.94), abstract -- -----	1-17

SA 97850

INTERNATIONAL SEARCH REPORT
Information on patent family members

09/02/95

International application No.

PCT/US 94/10158

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5085215	04/02/92	AU-B- 630319 AU-A- 7081391 EP-A- 0448193 JP-A- 4221577	22/10/92 26/09/91 25/09/91 12/08/92
US-A- 5144949	08/09/92	AU-A- 1586592 EP-A- 0559847 WO-A- 9216258	21/10/92 15/09/93 01/10/92
US-A- 5342405	30/08/94	AU-A- 1855892 EP-A- 0526798 JP-A- 5192416 US-A- 5269299 US-A- 5301669 AU-A- 5078493 EP-A- 0598615 JP-A- 6197993	11/02/93 10/02/93 03/08/93 14/12/93 12/04/94 02/06/94 25/05/94 19/07/94
US-A- 5350409	27/09/94	EP-A- 0621055	26/10/94